the combination of ceftriaxone and amikacin is less costly than ceftazidime plus amikacin, piperacillin/tazobactam plus amikacin, and meropenem. However, it should be stressed that the choice of antibiotic regimen should be based primarily on clinical and epidemiologic considerations; that is, in a setting of high risk of *Pseudomonas aeruginosa* infections, an antipseudomonal beta-lactam antibiotic should be preferred.

New aspects of cystic fibrosis, lung infection and inflammation

S239 Defensins in cystic fibrosis (CF)

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Because *Pseudomonas aeruginosa* represents an imminent threat to patients with CF but not healthy persons, we addressed the question what keeps normal lungs free of *P. aeruginosa* infection. Based on the working hypothesis that lung epithelial cells secrete *P. aeruginosa* killing peptide antibiotics, we isolated from supernatants of *P. aeruginosa*-stimulated lung epithelium cell line U549 a 4-kDa *P. aeruginosa* killing peptide, which is identical to human ß-defensin 2 (hBD-2), a defensin we recently discovered in inflamed skin. Natural hBD-2 strongly killed *P. aeruginosa* (LD_{90}:10 mg/L), but not *Staphylococcus aureus* (growth inhibition at concentration 100 mg/L). In contrast to all known human defensins, hBD-2 synthesis is inducible in epithelial cells by contact with bacteria or pro-inflammatory cytokines, which is supported by analyses of the promoter region of the hBD-2 gene. Because in CF it is believed that increased NaCl concentrations may affect antimicrobial activity of endogenous peptide antibiotics, we investigated the salt sensitivity of hBD-2 and found a dose-dependent inhibition of *P. aeruginosa* killing activity (IC_{50}: ~80 mM), indicating that hBD-2 is salt sensitive at physiologic ion strength. Investigation for hBD-2 in sputum of CF patients revealed immunoreactive hBD-2, indicating that hBD-2 production is not defective in CF. Systematic screening of CF patients' sputum for antimicrobial activity, however, revealed—apart from known defensins 1–3 and lysozyme—a number of as yet not identified molecules that might be important in antimicrobial defense in CF.

S240 Epithelial cell interactions involving CFTR and bacterial pathogens

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The CF transmembrane conductance regulator (CFTR) plays a critical role as a receptor involved in the lung's response to *Pseudomonas aeruginosa*. The absence of CFTR protein in most severe cases of CF results in decreased clearance of *P. aeruginosa* from the lung in the early stages of infection. We have recently determined that under the right conditions CF mice are hypersusceptible to oropharyngeal colonization by *P. aeruginosa* from environmental sources as well as experimentally induced *P. aeruginosa* lung infection. All mice exposed to *P. aeruginosa* in drinking water become colonized in the oropharynx, but once the contaminated water is removed, both wild-type and heterozygote *F508 Cftr mice clear the colonization, whereas CF mice remain colonized for prolonged periods. Introduction of *P. aeruginosa* enmeshed in alginate beads into the lungs of CF mice results in long-term infection accompanied by significant changes in pulmonary obstruction, whereas mice with at least one wild-type Cftr gene clear this infection. CFTR is also utilized by *Salmonella typhi* as a receptor for translocation from the gastrointestinal tract. Recent studies in CF mice with a G551 D allele indicate that this Cftr mutation results in decreased uptake of both *S. typhi* and *P. aeruginosa* by homozygote G551 D and heterozygote G551 D mice compared with wild-type mice. This is identical to results reported for *F508 Cftr mice. Overall, CFTR is an important receptor for both *P. aeruginosa* and *S. typhi*, and changes in CFTR protein due to different gene mutations can result in a similar phenotype in regard to susceptibility and resistance to *P. aeruginosa* and *S. typhi* infections.

S241 Neutrophil–parasite interactions

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Most patients with cystic fibrosis (CF) suffer from chronic endobronchial *Pseudomonas aeruginosa* infections. The lung tissue damage is caused by continuous activation of the immunologically specific inflammatory defense mechanisms of the lungs initiated by the antibody response and dominated by polymorphonuclear neutrophil leukocytes and their proteolytic and oxidative products. This inflammation induces a phenotypic shift from non-mucoid to mucoid, alginate-producing phenotypes of *P. aeruginosa* which then grow as a biofilm endobronchially. Such biofilms are impossible to eradicate with antibiotics. Currently used treatment strategies are chronic suppressive antibiotic treatment against *P. aeruginosa* and use of anti-inflammatory drugs such as inhaled budesonide or systemic treatment with ibuprofen or piroxicam. The immune response responsible for the tissue damage mimics a Th2 response, and animal experiments suggest that a shift to a Th1-like response by, for example, gamma-interferon treatment, may delay the tissue damage. Clinical trials have, however, not yet been carried out with gamma-interferon treatment.

S242 Bacterial vaccines in cystic fibrosis

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In patients with cystic fibrosis (CF), *Pseudomonas aeruginosa* and *Staphylococcus aureus* cause chronic pulmonary infections which are difficult to treat with antibiotics. Loss of lung function is the major cause of death in CF. Vaccination is a possible way to prevent these infections, and several antigens, including *P. aeruginosa* flagella and *S. aureus* exopolysaccharides, are promising vaccine candidates. In vitro and animal studies showed that flagella antigens were protective in compromised animals. Phase 1 studies using Immuno s flagella vaccines in healthy individuals and CF patients revealed that these vaccine preparations were well tolerated, showed no adverse side effects and gave rise to high and long-lasting antibody titers in the circulation of the individuals. Furthermore, immunization with a flagella vaccine elicited specific anti-flagellar antibodies not only systemically, but also in the secretory immune system of the airways. Consequently, a phase III multicenter vaccine trial using the *P. aeruginosa* 5142/1210-Flagella Vaccine IMMUNO was initiated. The study design is placebo-controlled, randomized and double-blind, involving about 500 CF patients without *P. aeruginosa* lung infection in 25 European CF centers.